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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,845	05/16/2006	Filippo Giancotti	MSK.P-076	7804

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,845	GIANCOTTI, FILIPPO	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 15-20* is/are pending in the application.

4a) Of the above claim(s) *6,10,16,18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,15,17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/25/06&12/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 and 15-20 are pending.

2. Applicant's election of Group I, claims 1-5, 7-9, 15, 17 and 19, drawn to a method for inhibition of angiogenesis in a tissue expressing α6β4 integrin, comprising the steps of exposing the tissue to a therapeutic agent effective to reduce the amount of active α6β4 integrin in the tissue, wherein the therapeutic agent targets β4, wherein the therapeutic agent is an antibody filed on 2/12/08, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 6, 10, 16, 18 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-5, 7-9, 15, 17 and 19 are under examination as they read on a method for inhibition of angiogenesis in a tissue expressing α6β4 integrin, comprising the steps of exposing the tissue to a therapeutic agent effective to reduce the amount of active α6β4 integrin in the tissue, wherein the therapeutic agent targets β4, wherein the therapeutic agent is an antibody.

5. Applicant's IDS, filed 10/25/06 and 12/12/06, is acknowledged, however, US 2003/0224993 reference, filed 12/12/06 was crossed out because it is duplicate of the same reference filed on 10/25/06.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5, 7-9, 15, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide **enablement** a method for inhibition of "angiogenesis in a tissue expressing α6β4 integrin", comprising the steps of exposing the tissue to a therapeutic agent effective to reduce the amount of active α6β4 integrin in the tissue, wherein the therapeutic "agent targets β4" in claim 1, wherein the angiogenesis to be inhibited is pathological angiogenesis in claim 4 or a method for "treatment of a disease condition associated with pathological angiogenesis" in a patient, comprising the step of administering to the patient an amount of a therapeutic agent effective to reduce the amount of active α6β4 integrin, wherein

the "therapeutic agent targets β4" in claim 7, wherein the agent is antibody in claim 5, 9, 15, 17 and 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

No working empirical data demonstrating that the claimed anti-β4 antibody would inhibit angiogenesis in a tissue expressing α6β4 integrin or treat a disease condition associated with pathological angiogenesis. The specification provides no single example to indicate the function of claimed anti-β4 antibody. Kennel et al (J. Cell Biol. 101:145-150, 1992) teach that β4 integrin subunit express on endothelium of larger vessels but not capillaries in lung, vessels in thymus, spleen and Peyer's patches, and portal vessels but not the central veins of the liver, are positive (see abstract in particular). Sepp et al (J. Invest. Dermatol. 104 :266-270,1995) teach that fibroblast growth factor induces changes in the levels and surface distribution of endothelial cell β4 integrins *in vitro*. Sepp et al teach that β4 is preferentially located on the basal surface of endothelial cells adjacent to basement membrane *in vivo* and *in vitro*, and the expression of integrins containing the β4 integrin subunit is decreased by treatment of HDMEC with angiogenic factors *in vitro* (see abstract in particular). Ngugen et al (Hum Pathol. 35(6):739-44, 2004) teaches that the β4 integrin may play a key role in angiogenesis via integrin-mediated signal transduction, putatively resulting in an arrest of endothelial proliferation (see page 742, 2nd col.,). α6β4 is not expressed during developmental angiogenesis (see Hiran et al, IDS reference). Finally, Lipscomb et al (*Cancer Research* 65:10970-10976, 2005) teach that an issue that arises from the foregoing discussion is whether α6β4-induced VEGF expression in breast carcinoma cells stimulates tumor angiogenesis. Although Lipscomb et al did not observe gross differences in the vasculature between control and ß4-deficient tumors, Lipscomb et al cannot exclude some effect of α6β4-expression on angiogenesis in these experiments. With this in mind, recent studies have examined the expression of α6β4 on endothelial cells and its possible role in angiogenesis. Based on the analysis of α6β4 expression in vascular endothelial cells during the development of the mouse whisker pad, it was inferred that this integrin actually inhibits the angiogenic switch (referring to Hiran's article). In contrast, another study argued that α6β4 promotes the migration and invasion of endothelial cells during the invasive phase of tumor angiogenesis (referring to Applicant's published work). Interestingly, however, loss of α6β4 signaling in the latter study did not affect tumor angiogenesis in an orthotopic model of mammary carcinogenesis, suggesting that the role of α6β4 in tumor angiogenesis may not be universal. Lipscomb et al concluded that more studies are warranted to assess the contribution of α6β4 to angiogenesis in breast tumors (see page 10975, 2nd col.). Thus, absent a positive

correlation between anti-β4 antibodies and angiogenesis, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

The instant specification discloses that mice with a targeted deletion of the β4 subunit cytoplasmic tail did not show any vascular defects during development. However, these mice have a highly reduced angiogenic response to bFGF and VEGF. In vitro studies showed that α6β4 did not affect proliferation of endothelial cells but was required for normal adhesion and migration. Tumor growth in these animals was suppressed, as was tumor angiogenesis. *Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The specification fails to provide agents such as anti-β4 antibodies or β4 RNAi that blocks activate signal transduction of β4 integrin that can be used in the claimed method. The specification does not provide empirical data to show the efficacy of anti-β4 antibody on angiogenesis or disease associated with a pathological angiogenesis, wherein the anti-β4 antibody would function as inhibitor of angiogenesis. It is not clear that the skilled artisan could predict the efficacy of the anti-β4 antibody, encompassed by the claims. The state of the art is that anti-β4 integrin antibodies enhance migratory and invasive abilities of human colon adenocarcinoma cells *in vivo* (a disease condition associated with pathological angiogenesis) (see Daemi et al. *Int. J. Cancer:* **85,** 850–856 (2000).

Since mice animals with targeted deletion of the β4 subunit cytoplasmic tail and α6β4 transfected endothelial cells were used as model system to show inhibition of tumor growth and tumor angiogenesis. It is not clear that reliance on this model accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively reach any therapeutic endpoint in mammals including human by administrating the therapeutic anti-β4 antibody. The specification does not teach how to extrapolate data obtained from a mice model of targeted deletion studies to the development of effective in vivo mammalian therapeutic treatment of angiogenesis, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the medicament exemplified in the specification.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 1-5, 7-9, 15, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a method for inhibition of "angiogenesis in a tissue expressing α6β4 integrin", comprising the steps of exposing the tissue to a therapeutic agent effective to

reduce the amount of active α6β4 integrin in the tissue, wherein the therapeutic "agent targets β4" in claim 1, wherein the angiogenesis to be inhibited is pathological angiogenesis in claim 4 or a method for "treatment of a disease condition associated with pathological angiogenesis" in a patient, comprising the step of administering to the patient an amount of a therapeutic agent effective to reduce the amount of active α6β4 integrin, wherein the "therapeutic agent targets β4" in claim 7, wherein the agent is antibody in claim 5, 9, 15, 17 and 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (tissue expressing α6β4 integrin, agent targets β4, pathological angiogenesis in a tissue expressing α6β4 integrin) to describe the claimed genus, nor does it provide a description of structural features that are common to species (tissue expressing α6β4 integrin, agent targets β4, pathological angiogenesis in a tissue expressing α6β4 integrin). The specification provides no structural description of tissue expressing α6β4 integrin, agent targets β4, pathological angiogenesis in a tissue expressing α6β4 integrin other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed tissue expressing α6β4 integrin, agent targets β4, pathological angiogenesis in a tissue expressing α6β4 integrin looks like. The specification's disclosure is inadequate to describe the claimed genus of tissue expressing α6β4 integrin, agent targets β4, pathological angiogenesis in a tissue expressing α6β4 integrin.

The specification fails to provide anti-β4 antibodies or RNAi that blocks activate signal transduction that can be used in the claimed method.

Applicant has disclosed only anti-β4 antibody; therefore, the skilled artisan cannot envision all the contemplated agent possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

10. Claims 1-5, 7-9, 15, 17 and 19 are rejected under 35 U.S.C. 102(e)/(b) as being anticipated by US 20030224993 (IDS reference)/WO 02/30465.

The `993 publication teaches and claims methods of inhibiting proliferation of cancer cell selected from the group consisting of melanoma, adenoma, lymphoma, myeloma, carcinoma, plasmocytoma, sarcoma, glioma, thyoma, leukemia, skin cancer, retinal cancer, breast cancer, prostate cancer, colon cancer, esophageal cancer, stomac cancer, pancreas cancer, brain tumors, lung cancer, ovarian cancer, cervical cancer, hepatic cancer, gastrointestinal cancer, and head and neck cancer cells (pathological angiogenesis diseases as evidenced by published claims 125-126) comprises contacting a B4 integrin with a composition that inhibits ligand binding (see published claims 1, 2, 10, 13, 38, 41, 45, 106, 121-126 in particular), such as antisense molecules to beta4 mRNA (see published claims 28-29 in particular). The `993 publication teaches that antibodies can be used as integrin inhibitor (see ¶¶ 47-48 in particular).

While the prior art disclosure may be silent as to the "inhibiting angiogenesis" per se; the instant claims merely recite newly discovered results of "inhibiting angiogenesis" of a known method of

treating the same patients with the β4-specific antibodies. The claim language is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. It is noted that VEGF produced by cancer cells would positively affect angiogenesis.

The WO `465 publication corresponds to the US `993 Application.

The reference teachings anticipate the claimed invention.

10. Claims 1-5, 7-9, 15, 17 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by US 20060172957.

The `957 publication teaches and a method of treating an animal having a disease or condition associated with Integrin beta 4 binding protein comprising administering to said animal a therapeutically or prophylactically effective amount of the compound comprising antisense nucleic acid molecule so that expression of Integrin beta 4 binding protein is inhibited (see published claim 16), wherein the disease or condition is a hypoproliferative disorder (see published claim 17), wherein the hypoproliferative disorder is cancer (associated with angiogenesis) (see published claim 18), wherein the cancer is colorectal (see published claim 19). The `957 publication teaches that strategies aimed at investigating integrin beta 4 binding protein function have involved the use of antibodies (see ¶9). It is noted that VEGF produced by cancer cells would positively affect angiogenesis.

While the prior art disclosure may be silent as to the "inhibiting angiogenesis" per se; the instant claims merely recite newly discovered results of "inhibiting angiogenesis" of a known method of treating the same patients with the β4-specific antibodies. The claim language is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims.

The reference teachings anticipate the claimed invention.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

12. Claims 1-5, 7-9, 15, 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Enenstein and Kramer (J Invest Dermatol. 1994 Sep;103(3):381-6).

Enenstein and Kramer suggest an important role for the α6β4 integrin in the initial stages of endothelial outmigration during new vessel growth (angiogenesis). Enenstein and Kramer teach that α6 and β4 were consistently found along the whole length of capillary loops and extended to

the distal ends of presumed sprouts (see abstract). Enenstein and Kramer also teach that if integrins function in cord formation *in vivo*, one would expect that a major component would be some non-β1 integrin, such as β4. (see DISCUSSION in particular). Enenstein and Kramer teach the use of mAb anti-β4 (3E1) (see page 382, under antibodies). Enenstein and Kramer teach that angiogenesis associate with development or wound healing, blood vessel growth and repair (see page 381, introduction).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to consider blocking tube formation by anti-β4 antibodies taught by Enenstein and Kramer in mammalian subject including humans.

Given that β4 was consistently found along the whole length of capillary loops and extended to the distal ends of presumed sprouts and that the β4 integrin subunit function in cord formation in vivo, one of ordinary skill in the art at the time the invention was made would have been motivated to do so because the inhibition tube formation using the anti-β4 antibodies taught by Enenstein and Kramer et al and further, Enenstein and Kramer et al suggest the in vivo treatment implicitly.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 31, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644